REMARKS

In the Office Action dated November 17, 2004, claims 1-38, 40-52 and 54-61 are pending. Claims 1-37 and 40-52 have been withdrawn from consideration. Claims 38 and 54-61 are under examination. Claim 61 is objected to because of certain alleged informalities. Claims 54-61 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 38 and 54-58 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tachado et al. (*Journal of Immunology* 156: 1897-1907, 1996). Claims 38 and 54-56 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tachado et al. (*BBRC* 205/2: 984-991, 1994) or Richardson et al. (*Insect Molecular Biology* 1/3: 139-147, 1993). Claims 38 and 54-58 are also rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tachado et al. (*PNAS* 94: 4022-4027, 1997) or Schofield et al. (*Journal of Immunology* 156: 1886-1896, 1996). Claims 38 and 54-61 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement.

This Response addresses each of the Examiner's rejections and objections. Applicant therefore respectfully submits that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

In the Office Action, the Examiner has made the Restriction Requirement final. Consequently, claims 1-37 and 40-52 are withdrawn from consideration. By way of the instant amendment, Applicant has canceled claims 1-37 and 40-52 without prejudice. Applicant reserves the right to pursue the subject matter of the canceled claims in one or more divisional applications.

Claim 61 is objected to allegedly because several of the GPI inositolglycan domains are spelt incorrectly.

Applicant has amended claim 61 to correct the typographical errors. Support for the amendment to claim 61 is found in the specification and in original claim 32. Withdrawal of the objection to claim 61 is therefore respectfully requested.

Claims 54-61 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Specifically, the Examiner objects to the recitation of "insufficient" and questions the extent of a lipidic domain that is present in the modified GPI molecule.

In response, Applicant respectfully submits that the claims clearly delineate that the extent of the lipidic domain that remains in the modified GPI molecule is such that the residual lipidic domain, if any, is insufficient to induce or elicit an immune response to a GPI lipid domain. Applicant respectfully submits that in light of the teaching in the specification, the meaning of the recitation "insufficient" is clear to those skilled in the art. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is therefore respectfully requested.

Claims 38 and 54-58 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tachado et al. (*Journal of Immunology* 156: 1897-1907, 1996) ("Tachado (1996)").

According to the Examiner, Tachado (1996) discloses a GPI from *Plasmodium falciparum*, which GPI induced an immune response. The Examiner further states that: "Although Tachado (1996) does not specifically disclose that the lipidic domain is incapable of inducing an immune response, it would appear that no immune response is induced directed to the lipidic domain of the GPI." Furthermore, the Examiner states that because the claims recite "derivative or equivalent" of a modified GPI, which is defined broadly in the specification, the claims read on the GPI molecule disclosed by Tachado (1996). The Examiner states that the burden is on Applicant to show a distinction between the claimed composition and the composition of the prior art.

Applicant respectfully disagrees with the Examiner's rejection. Applicant respectfully submits that the present invention is predicated in part on the determination that GPI or a GPI-derived glycan or inositolglycan can be used as a vaccine or a vaccine target. Prior to the present application, the development of vaccines against parasites had focused on the use of proteins to elicit an immune response. The present inventor was the first to determine the immunogenic properties of GPI or a GPI-derived glycan or inositolglycan and to recognize the potential of utilizing sugars in vaccine development.

More specifically, the present inventor has surprisingly found that mice immunized with intact GPI mount an IgM-dominated response, directed predominantly to the lipidic domain of the molecule. IgM antibodies generated in such a response cross-reacts with host GPI lipidic domains that are exposed at host cell surfaces, and are not protective clinically against subsequent parasite infection. In fact, passive transfer of these antibodies exacerbates disease severity during subsequent parasite infection. In contrast, immunization with the glycan domain of malarial GPI results in IgG antibodies interactive with the glycan domain of GPI. Immunized mice are substantially protected against subsequent malaria challenge. Passive transfer of the IgG antibodies is protective against subsequent malaria challenge. Therefore, the inventor has demonstrated that IgM antibodies to the lipidic domain and IgG antibodies to the glycan domain of the malaria GPI differ in their effects, the former promoting disease and the latter preventing it.

Turning to Tachado (1996), this reference simply discloses that an intact GPI from *Plasmodium falciparum* induced an immune response. Based on the findings disclosed in the present application, the immune response shown in Tachado (1996) may very well be an IgM-dominated response directed to the lipidic domain of GPI. There is absolutely no basis for the

Examiner to conclude that the immune response was not directed to the lipidic domain of the GPI. In this connection, Applicant respectfully submits that the fact that a certain characteristic may be present in the prior art is not sufficient to establish the inherency of that characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (emphasis added).

Applicant further respectfully submits that, as disclosed and claimed in the present application, the GPI molecule is modified such that the modified GPI molecule does not induce an immune response to the lipidic domain (claim 38). In a preferred embodiment (claim 54), the lipid domain has been partially or fully removed such as the modified GPI molecule has insufficient lipidic domain to induce an immune response towards the lipid domain of an otherwise intact GPI molecule. Tachado (1996) does not teach or suggest modifying GPI by partially or fully removing the lipid domain. In fact, the GPI molecule employed by Tachado (1996) appears to be an intact GPI molecule. Applicant submits that a rejection of a claim under 35 U.S.C. §102(b) requires that the single prior art reference disclose every element of the claim. The absence from the reference of any claimed element negates anticipation. Kloster Speedsteel AB v Crucible Inc., 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986). In the present case, Tachado (1996) does not teach a modified GPI molecule that does not induce an immune response to the lipidic domain or that has insufficient lipidic domain to elicit an immune response.

In view of the foregoing, it is respectfully submitted that the claimed invention is not anticipated by Tachado (1996). Withdrawal of the §102(b) rejection based on Tachado (1996) is therefore respectfully requested.

Claims 38 and 54-56 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tachado et al. (*BBRC* 205/2: 984-991, 1994) (hereinafter "Tachado (1994)"), or by Richardson et

al. (*Insect Molecular Biology*, 1/3: 139-147, 1993) (hereinafter "Richardson").

According to the Examiner, Tachado (1994) discloses a GPI from a microorganism as well as a mAb raised against the GPI.

Applicant respectfully submits that similar to Tachado (1996), Tachado (1994) employed an intact GPI molecule. Tachado (1994) does not teach or suggest, implicitly or explicitly, a modified GPI molecule that lacks the lipidic domain and that induces an immune response against the glycan domain of the molecule and does not induce an immune response to the lipid domain of the intact GPI.

With respect to the Richardson reference, the Examiner contends that this reference discloses a recombinant protein linked to a GPI membrane anchor, which showed strong protective activity against ticks in cattle vaccinated with this protein. The Examiner states that the recombinant protein is considered to be a derivative of the GPI. The Examiner also alleges that Figure 1, lane 3 of the Richardson reference discloses that an antibody against GPI was developed.

Applicant respectfully submits that the presently claimed composition induces an immune response towards the glycan domain of a GPI molecule, whereas Richardson (1993) is directed to inducing an immune response towards an antigenic protein, which under natural conditions has a GPI anchor. It is abundantly clear that the immune response provoked in Richardson (1993) was directed towards the protein portion of the molecule, rather than the GPI anchor of the molecule. In fact, the authors intended to exclude the GPI anchor from their vaccine and described a method of producing the target protein lacking a GPI in the reference. The authors further state:

> "...the GPI anchor is not essential for the expression of the protective

> immunological response..." and "...the production of BM86trun (i.e. lacking GPI) as a secreted form of BM86 allows efficient recovery and purification of relatively large quantities of this recombinant protein.

Moreover, the authors note:

> "recombinant BM86 was originally expressed as an inclusion body in *E. coli*...this form... did induce a strong immunological response...This result rules out a major involvement of carbohydrate residues on BM86 in the protective response as recombinant proteins produced in bacteria are not glycosylated."

Therefore, Richardson does not teach or suggest a modified GPI, which includes a glycan domain but lacks sufficient lipid domain and which induces an immune response specifically directed to the glycan domain.

In view of the foregoing, it is respectfully submitted that the claimed invention is not disclosed by either Tachado (1994) or Richardson. Withdrawal of the §102(b) rejection based on these references is respectfully requested.

Claims 38 and 54-58 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tachado et al. (*PNAS* 94: 4022-4027, 1997) ("Tachado (1997)") or Schofield et al. (*Journal of Immunology* 156: 1886-1896, 1996) ("Schofield").

According to the Examiner, Tachado (1997) discloses GPI-anchored surface proteins and a mAb to the GPI. The Examiner also alleges that Tachado (1997) discloses derivatives or precursors of the GPI (see Materials and Methods). Regarding Schofield, the Examiner contends that this reference discloses a GPI of a malaria parasite origin and a mAb to the malarial GPI.

Applicant respectfully submits that Tachado (1997) and Schofield merely disclose intact GPI molecules or precursors thereof. These references do not teach or suggest, implicitly or explicitly, a modified GPI molecule that lacks the lipidic domain and that induces an immune

response against the glycan domain of the molecule and does not induce an immune response to the lipid domain of the intact GPI.

In view of the foregoing, it is respectfully submitted that the claimed invention is not disclosed by either Tachado (1997) or Schofield. Withdrawal of the §102(b) rejection based on these references is respectfully requested.

Claims 38 and 54-61 are rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enabling support in the specification.

The Examiner acknowledges that the specification teaches in Example 16, page 66, that all of the mice, which were immunized with free GPI, died upon challenge with *P. berghi*. The immunization of mice with free GPI generated IgM reacting with the PI domain of GPI, and appeared to have exacerbated the *P. berghi* cerebral malaria syndrome. The Examiner also acknowledges that Example 17 of the specification on page 67 teaches that immunization of mice with GPI-glycan-KLH and IFA protected 57% of mice upon parasite challenge. Additionally, the specification shows that a protection rate of 95% was achieved when mice were immunized with anti-GPI glycan-KLH (passive immunization). However, the Examiner contends that the specification does not provide enablement for a composition that comprises only a modified GPI. Further, the Examiner indicates that the claims do not define how the GPI has been modified. Moreover, the Examiner contends that the specification does not provide enablement for any of the specifically claimed GPIs as set forth in claims 59-61. Thus, the Examiner concludes that it would require undue experimentation for those skilled in the art to practice the claimed invention.

Applicant respectfully submits that contrary to the Examiner's allegation, the claims define how a GPI molecule has been modified. Specifically, as defined in claim 38, a modified

GPI molecule induces an immune response directed to the inositolglycan domain but is incapable of inducing an immune response directed to the lipidic domain of an otherwise intact GPI. As disclosed in the specification, an intact GPI induces immune responses predominantly directed towards the lipidic domain. Such immune responses directed towards the lipidic domain are not protective against parasite infection, and as acknowledged by the Examiner, exacerbate the malaria syndrome upon subsequent infection. However, as disclosed in the specification, a GPI molecule can be modified to partially or fully remove the lipidic domain such that the remaining lipidic domain, if any, is incapable to elicit an immune response (as characterized in claim 54), and the modified GPI induces an immune response specifically directed towards the inositolglycan domain. The present inventor has uniquely recognized that immune responses specifically directed towards the inositolglycan domain are capable of protecting the recipient against subsequent parasite infection. Provided with this unique recognition of the present application, those skilled in the art are able to modify a GPI molecule by routine techniques, and to determine by using routine procedures whether or not a modified GPI molecule induces immune responses towards the lipid domain of the intact GPI. Furthermore, the examples of the present application (pages 58-60) describe how to obtain the glycan portions of GPI molecules, i.e., devoid of the lipid domain of GPI.

The Examiner has also alleged that the specification does not provide enablement for a composition that comprises only a modified GPI. Applicant respectfully submits that the specification discloses that the inositolglycan domain of a GPI molecule can be conjugated to another molecule, such as a carrier protein or other vaccine molecules. See page 22 of the specification. Conjugation of small molecules to carrier proteins for the purpose of provoking an immune response towards the small molecules is routinely practiced by those skilled in the art,

and is not critical to the claimed invention. Therefore, Applicant should not be required to include the feature of a carrier molecule in the claims. In any event, the specification has demonstrated that immune responses are induced specifically directed towards the inositolglycan domain of a GPI molecule. The key feature of the claimed invention, i.e., a modified GPI molecule capable of inducing an immune response towards the inositolglycan domain, is recited in the claims.

Regarding claims 59-61, Applicant respectfully submits that the specification has specifically demonstrated that immune responses are induced towards the glycan domain of a GPI molecule. As described in the specification on page 13, lines 5-20, GPIs consist of a conserved core glycan, Manα1,2 Manα1,6 Manα1,4 GlcN, linked to the 6-position of the myo-inositol ring of phosphatidylinositol (PI). The tetrasaccharide core glycan may be further substituted with sugars, phosphates and ethanolamine groups in a species and tissue-specific manner. In view of the teaching in the specification, those skilled in the art would be able to produce a modified GPI which contains a glycan structure as characterized in claims 59-61 and to elicit an immune response with such modified GPI, without undue experimentation.

In view of the foregoing, it is respectfully submitted that based on the present teaching, those skilled in the art are able to practice the claimed invention without undue experimentation. Therefore, the enablement rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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